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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/768,729	01/28/2004	Yi-Ju Chen	21465-509 UTIL	8174

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EXAMINER	
THOMAS, DAVID C	
ART UNIT	PAPER NUMBER
1637	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/25/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

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Office Action Summary	Application No.	Applicant(s)	
	10/768,729	CHEN ET AL.	
	Examiner	Art Unit	
	David C. Thomas	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *2-35* is/are allowed.

6)☒ Claim(s) *1 and 36-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *30 June 2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election of species in the reply filed on October 30, 2006 is acknowledged. Applicants elect, with traverse, the primer blocking species PO_4 generic to claims 1, 4, 28, and 31. Applicants further elect, also with traverse, the modified nucleotide 5-hydroxy-uracil generic to claims 1, 11, and 12. The traversal in both cases is on the grounds that there is no burden in searching all of the species and that the species in each group share a common utility or substantial structural feature. This is not found persuasive for the following reasons. A chemical and word search would be required for each primer blocking species, which are also chemically distinct molecular groups. A chemical and word search would also be required for each modified base, which also represent chemically distinct molecules with unique side groups.

The requirement is still deemed proper and is therefore made FINAL. Claims 1-39 will be examined on the merits.

Double Patenting

2. Claim 1 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 8 and 83 of copending Application No. 10/767,779 (U.S. Patent Pub. 2005/0130173). Although the conflicting claims are not identical, they are not patentably distinct from each other because both read on methods of sequencing a nucleic acid molecule comprising the same steps, including the use of blocked primers for sequencing two or more target regions.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 36-38 are rejected under 35 U.S.C. 102(a) as being anticipated by Murphy et al. (Amer. J. Pathol. (2002) 161:27-33).

Murphy teaches a method of sequencing a nucleic acid molecule comprising the steps of:

(a) hybridizing a sequencing primer to one strand of the nucleic acid molecule (a primer is hybridized to a template PCR product, p. 28, column 2, lines 34-37 and Figure 1A);

(b) incorporating at least one base onto said one strand of the nucleic acid by polymerase elongation from said sequencing primer (primer is extended during cycle sequencing, p. 28, column 2, lines 5-9 and 39-42);

(c) preventing further elongation of said primer (products are terminated either by addition of nucleotide from the termination mix or by reaching the end of the template, p. 28, column 2, lines 5-9 and 39-42 and Figure 1A);

(d) repeating steps (a) to (c) on the same strand of nucleic acid or on a different strand of nucleic acid until a desired amount of sequence is determined (additional primers are used simultaneously to generate sequencing products of different lengths resolvable by capillary electrophoresis on a ABI Prism 3700 sequencing system, p. 28, column 1, lines 28-29, p. 28; column 2, line 34 to p. 30, column 1, line 13, and Figure 1B-E).

With regard to claim 37, Murphy teaches a method wherein said step (c) of preventing further elongation comprises

(a) completing the elongation from the unblocked primer with polymerase and dNTPs (extension of some molecules is completed to the end of the template, p. 28, column 2, lines 39-42); or

(b) terminating the elongation with polymerase in a manganese containing buffer, dNTPs, and at least one ddNTP (some molecules are terminated by incorporation of terminating nucleotide in termination mix to generate variety of products useful for reading a sequence, p. 28, column 2, lines 5-9 and 37-42 and Figure 1B-E).

With regard to claim 38, Murphy teaches a method further comprising the step of removing said polymerase, dNTPs, and ddNTPs after said preventing step (DNA fragments were separated on a capillary gel sequencing system, which removes reagents such as the polymerase, dNTPs, and ddNTPs, p. 28, column 1, lines 28-29).

5. Claims 36-38 are rejected under 35 U.S.C. 102(b) as being anticipated by Wiemann et al. (Anal. Biochem. (1996) 234:166-174).

Wiemann teaches a method of sequencing a nucleic acid molecule comprising the steps of:

(a) hybridizing a sequencing primer to one strand of the nucleic acid molecule (a primer is annealed to a strand of DNA, p. 168, column 1, lines 8-10 and Figure 1, second step);

(b) incorporating at least one base onto said one strand of the nucleic acid by polymerase elongation from said sequencing primer (one labeled nucleotide is incorporated onto the primer, p. 168, column 1, lines 10-14 and Figure 1, third step);

(c) preventing further elongation of said primer (after incorporation of the first labeled dNTP, the polymerase pauses and does not proceed further owing to the low concentration of labeled dNTPs and lack of other dNTPs, p. 168, column 2, lines 2-8);

(d) repeating steps (a) to (c) on the same strand of nucleic acid or on a different strand of nucleic acid until a desired amount of sequence is determined (a labeled dNTP is added to another primer on the same strand or another strand of DNA, p. 168, column 1, line 6 to column 2, line 8 and Figure 1, steps 1-3).

With regard to claim 37, Wiemann teaches a method wherein said step (c) of preventing further elongation comprises

(a) completing the elongation from the unblocked primer with polymerase and dNTPs (after incorporation of the first labeled dNTP, the polymerase pauses and does not proceed further owing to the low concentration of labeled dNTPs and lack of other dNTPs, p. 168, column 2, lines 2-8); or

(b) terminating the elongation with polymerase in a manganese-containing buffer, dNTPs, and at least one ddNTP (following the labeling step, extension buffer containing manganese chloride can be added to allow further extension and termination using a different ddNTP in each of four termination reactions, page 167, column 2, lines 5-17 and Figure 1, step 4).

With regard to claim 38, Wiemann teaches a method further comprising the step of removing said polymerase, dNTPs, and ddNTPs after said preventing step (DNA fragments were separated on a sequencing gel, which removes reagents such as the polymerase, dNTPs, and ddNTPs, p. 167, column 2, lines 38-47).

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claim 39 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wiemann et al. (Anal. Biochem. (1996) 234:166-174) in view of Ronaghi et al. (Anal. Biochem. (1999) 267:65-71) and further in view of Jin (U.S. Patent No. 6,124,100).

Wiemann teaches the limitations of claims 36-38 as discussed above.

Wiemann does not teach a method of sequencing a plurality of double stranded nucleic acid molecules comprising separating two strands of each double stranded nucleic acid and attaching each of the two complementary strands to a single bead prior to sequencing the two strands.

Ronaghi teaches a method of sequencing DNA wherein one of the strands is immobilized on a paramagnetic bead and sequenced, while the other strand is eluted by alkali treatment and sequenced in solution (p. 66, column 1, lines 13-24).

Ronaghi does not teach a method wherein both strands are immobilized on the same bead and wherein the identity of at least one base of both strands are determined.

Jin teaches a method of labeling both 5' ends of PCR products with biotin using two primers that are each labeled with biotin (column 5, lines 28-34).

Jin does not teach a method attaching the biotin-labeled primers to a bead and determining the identity of at least one base of both strands.

It would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to combine the methods of Wiemann, Ronaghi, and Jin since Wiemann teaches methods of sequencing two complementary strands of DNA simultaneously, Ronaghi teaches a method of sequencing one strand of DNA immobilized on a paramagnetic bead, while Jin teaches methods of labeling a double-

stranded DNA molecule such as a PCR product with biotin at both termini allowing both strands to be immobilized on a bead. Thus, an ordinary practitioner would have been motivated to combine these systems since Wiemann provides a highly powerful technology for sequencing complementary strands that doubles the output of sequencing while reducing costs associated with labeled primers (Wiemann, p. 166, column 2, lines 5-6 and p. 167, column 1, lines 3-13), while Ronaghi provides a method to immobilize biotinylated DNA strands on a streptavidin-coated paramagnetic bead (p. 66, column 1, lines 13-24) which allows easy purification of the template prior to sequencing. Finally, Jin teaches an easy method to label both strands with biotin to enable direct attachment of both strands to the same streptavidin-coated bead to be used in the method of Wiemann for simultaneous sequencing. Thus, a double-stranded molecule can be sequenced in one reaction using unlabeled primers, which reduces the cost of the reagents, while the products can be analyzed on the same instrument in parallel (Wiemann, p. 167, column 1, lines 3-13), which reduces instrument usage per sequence and generates the sequencing data more efficiently.

Allowable Subject Matter

9. Except for the double patenting issue raised above, claims 1-35 would be allowable since no prior art was found that teaches a method of sequencing a nucleic acid molecule comprising the steps of hybridizing an unblocked primer and one or more reversibly-blocked primers to a template, extending the unblocked primer and preventing further extension, deblocking one of the reversibly-blocked primers and elongating from it, and finally, preventing further extension from the second primer.

Conclusion

10. Claims 1-35 are allowable, while claims 36-39 are rejected.

Correspondence

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David C. Thomas whose telephone number is 571-272-3320. The examiner can normally be reached on 5 days, 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David C. Thomas
Patent Examiner
Art Unit 1637

1/19/07

JEFFREY FREDMAN
PRIMARY EXAMINER
1/18/07